# Acute Leukemia Q&A

**Tuesday, November 28, 2023**
**Dr. Patrick Stiff, Loyola Medicine**
**Dr. Farhad Ravandi, MD Anderson**

Hello everyone. Thank you for joining us today for the Q&A session on Acute Leukemias. My name is Kevin Radelet. I'm the Executive Director of the Leukemia Research Foundation, and we're excited to offer today's webinar and welcome to great experts in the field to answer your questions.

I would like to take a moment to provide you with a brief overview of the Leukemia Research Foundation. Our mission is to cure leukemia by funding innovative research and to support patients and families. Since 1946, we've raised over $87 million in support of our mission and have funded research grants to more than 600 new investigators worldwide to help them advance their research.

In addition to the research funding, the foundation supports patients and families by providing free programs and resources including educational programs, disease and treatment information, peer support programs, financial assistance, and a directory of other helpful organizations and resources. Our educational programs include our annual new and emerging treatments conference, today's Q&A session. Other programs, this year we'll be having a clinical trials presentation, a webinar in cancer and finances stem cell transplants and more.

Over this past year, we have been adding to and enhancing our leukemia disease information on our website, including the subtypes and other informational content, including treatments newly diagnosed and more. I encourage you to visit our website, which is leukemiarf.org, to check out these resources and to sign up for our email list if you haven't yet registered.

A special thanks today to our sponsors of today's Q&, including AbbVie, Bristol Myers Squibb, Daiichi Sankyo, Merck, and Novartis for helping to make this presentation possible. Now, we received a number of questions as part of the registration process, and we hope to address as many as possible as we go along. If we have time at the end, we'll accept questions via the chat dropdown at the bottom of your screen. Also, we are recording today's session and it will be sent out to everybody who registered as well as we're going to post it on our website in the days ahead.

We're honored today to have two esteemed panelists, Dr. Farhad Ravandi and Dr. Patrick Stiff. Dr. Ravandi is a Professor of Medicine and the chief section of the Developmental Therapeutics in the Department of Leukemia at the University of Texas MD Anderson Cancer Center. He graduated from the University of London and undertook residency and fellowship training at Baylor College of Medicine and the MD Anderson Cancer Center.

He then joined the University of Illinois Chicago as the Director of the Leukemia Program and the interim director of Stem Cell Transplant Program for three years until he joined the Leukemia Department at MD Anderson in 2003. Dr. Ravandi is board certified in internal medicine, hematology and medical oncology, and has authored several book chapters and many articles in peer reviewed journals.

Also, joining us today is Dr. Patrick Stiff, who's the Director of the Division of Hematology and Oncology at Loyola Medicine. He is the Coleman Professor of Oncology at Loyola University Stritch School of Medicine. He's also a Stritch school alumnus. Dr. Stiff is board certified as well in internal medicine, oncology and hematology.

He completed his residency in internal medicine at the Cleveland Clinic and was a research fellow at Memorial Sloan Kettering Cancer Center in New York. Also for many years, Dr. Stiff served as the chair of the Leukemia Research Foundation's Medical Advisory Board. So please welcome Dr. Ravandi and Dr. Stiff.

Thank you both for joining us today. I think that the best way to go about this, as I mentioned, is that we have many questions that were submitted during the registration process, so I'm just going to read some of those and then the two of you can go ahead with the answers to the questions. We'll try to go AML, ALL and then more general questions.

***But the first question I have is are there any clinical trials for patients that are 75 years of age for either AML or ALL that you're aware of?***

*Dr. Farhad Ravandi:*

If I may go ahead. Thanks very much actually for the invitation to be here. And with regards to the question, AML is actually a disease of the older population, so the median ages at diagnosis is about 68, so that means half of patients are 68 or 70 or older, and there is now a numerous number of clinical trials available for the older population with AML.

In fact, that's one of the areas of biggest development over the last five or six or seven years because we used to have to rely on traditional chemotherapy in these older patients, and because of the fact that as we all get older, we lose some of our body reserves and functions, so it becomes more difficult to tolerate chemotherapy.

So there are now a lot of research directly towards developing molecularly targeted treatments, which are generally much more tolerable. And in terms of transplant, I'm going to defer to Dr. Stiff. I'm sure he will have a better insight on that than I have.

*Dr. Patrick Stiff:*

Okay. Thank you also for having me join you all today and happy to help clear up the air for these diseases. So the question again, is there any clinical trials for patients 75 years and older? Actually over the last several years, the National Cancer Institute with the three major cooperative groups, the Alliance, the Southwest Oncology Group and the Eastern Cooperative Oncology Group have gotten together and have formed a new group of experts, if you will, that are going to tackle this problem. It's called MyeloMATCH.

And you'll hear more about this probably in the general press when these first set of trials becomes available early in 2024. Basically, as was already mentioned, there's a lot of heterogeneity in the disease and with most patients being above the age of 65 to 70, we are focusing not just on younger patients who are healthy with the de novo acute leukemia, but also on the elderly patients.

There's two types of patients that are elderly, those that are what we call fit and those that are not very fit. And so the clinical trials that you'll be seeing over the next year or two will focus on some of the genetic subtypes as well as the fitness of the patient in their ability to tolerate more aggressive therapy. I think all of us feel that over the last 40 years, the more aggressive therapy you give to patients, the better the outcome.

But pioneering work, especially done at MD Anderson has shown that some of these newer agents may be just as effective, if not more so than more effective

therapies that we've been using in the past for younger patients that are really dose intensive. And that lower dose therapies that are given more in a continuous fashion may be actually more efficacious. And so many of the treatments that we've developed over the last few years have gotten the backbone of a hypomethylating agent. One of them is called azacitidine, the other is called decitabine with a BCL2 inhibitor called venetoclax.

And now over time, we're going to start actually adding a third drug to these or exploring ways of modifying this two drug combination, focusing again on the elderly or the elderly unfit patient population. The unique thing about this set of trials is that it's truly a package and it will allow patients to really move on to a diagnosis and therapy very quickly.

Right now, if you have a patient with acute leukemia, there are a variety of tests that we do. Some of them may take a week or two weeks to get the results, and those results really do impact what treatments are given. So many patients that are coming in now with acute leukemia have to wait a bit before they can start therapy.

What's going to be part of the MyeloMATCH program is a intent to start therapy within the first three to five days after the diagnosis is made because there are going to be labs all over the country that are going to be working furiously quickly on getting the results to really subtype these patients with leukemia and then a central organized group that's going to be identifying which clinical trials are going to be available for patients with a specific genetic subtype.

It was about 20 years ago that we invited somebody world class leukemia doc here to give a lecture, and basically he shook his head and said, "Because there's so many different subtypes and so many different patients will never have a uniform treatment for acute leukemia." And that's true, but that doesn't mean that we can't subdivide in some of these groups that we're going to be treating maybe only five or 10% of the patients with leukemias and we'll be able to say, in this group of 40 patients with this subtype of leukemia, this new treatment did or did not do better than the standard of care.

So it's going to be an exciting time over the next year or two years as we get started with these clinical trials. So kind of a long answer, but if you have leukemia right now and you're above age 75, there are good treatments out there for you. But as we get into MyeloMATCH, things may actually move a little bit more quickly and we'll come to some answers a little bit faster than we have in the past.

***Kevin Radelet:***

**How about recommended treatments as you get into your mid 70s and older for both types of acute leukemias?**

*Dr. Farhad Ravandi:*

As it was mentioned, we are focusing more and more on effective better tolerated treatment. So even the standard of care for particularly patients who are considered not fit for chemotherapy is now as mentioned, a combination of this drug, venetoclax plus a hypomethylating agent, which is a relatively mild form of chemotherapy.

And also there are other regimens not totally different from that, that include one of the standard agents that has been used in AML called cytarabine at low doses, much more tolerable doses in addition to other agents. So there is actually outside clinical trials reasonably effective and well-tolerated therapy available for all the patients with AML.

Our group is also of interest in developing all oral therapy regimens that are just with oral agents rather than just giving it through the vein as chemotherapy has been given for a long time. So there are some trials, for example, of effective AML treatments that are all pills or tablets, and some of the early results of these trials are very exciting.

Of course it takes time before this becomes more and more of a standard approach. But again, just going back to what I said originally, even as a standard of care, there are now reasonably effective regimens available, at least for majority of AML patients. There are some subtypes that are still very difficult to treat.

*Dr. Patrick Stiff:*

I agree. I think again, in the past if we saw a patient who was 75 and was unfit, I think many times we would say the therapy that we have available is too toxic for you, and so we would recommend no therapy or therapy designed to improve your quality of life and really not quantity of life. And now we have treatments that are truly poised to increase patient's quantity of life.

And I would second the notion of the oral therapies. When we talk about low dose therapies for older patients, these are not given, come in and get your treatment and then go home for three weeks and then come back and get another treatment like we do for breast cancer. These are treatments that require daily therapy for five to seven days, sometimes as long as 10 days, and then they do impact the blood counts.

So patients are frequently going back and forth and back and forth to the hospital. And I've had several patients that after a couple months of this, they basically say, you know what, even if I'm in remission, this is just too much. The oral drugs may be the answer to that so that you can minimize the number of visits that you come back to see the doctors. And as was mentioned, the oral agents are just as effective in many cases as some of the subcutaneous or the intravenous drugs. So these are agents that may be of value.

Of course there's always the copays and part D and part C of Medicare for elderly patients, and certainly we advise patients to really check into their insurance coverage. Something given in the hospital or in the clinic is part B for Medicare and it's covered under part B. Oral medications are not covered under part B, they're covered under part D and obviously their copays, et cetera. So that does impact a bit on sometimes the decision. So we strongly recommend that patients talk to their team, and if they're interested in the oral drugs to make sure that there's not a huge financial hit

***Kevin Radelet:***

**When it comes to ALL more adolescent type of acute, How do you feel when a patient, they have never heard perhaps of leukemia and all of a sudden they get this diagnosis, do you highly recommend, do you recommend that they get second, third opinions?**

*Dr. Farhad Ravandi:*

I don't know how we are going to turn, but ALL is actually a very interesting disease these days because for a long time in childhood ALL, we were very successful in curing the vast majority of patients, over 90% of patients with the traditional standard chemotherapy agents that were available. But as the age increased, and when I say that even in the 20s and 30s, the cure fraction declined with the traditional chemotherapy strategies.

Over the last several years, there's been some major developments in ALL that have really completely transformed the management of this disease across the board. First was the development of immune-based strategies. So by that there are what we call antibodies that are directed against markers on the ALL cells, and some of these antibodies have payload that delivers it directly into the cells. Others are designed and develop to try to recruit the patient's immune system to attack these cells.

And in addition to that, there has been a major, major development of CAR T-cell therapies which are also highly effective, and I would say revolutionary in the

management of relapsed ALL patients. Another thing that has been developed in ALL therapy, which is I think highly important is one better understanding that subtypes of ALL and also a better way of monitoring residual disease burden in ALL something people refer to as measurable residual disease, which is just detectable amount of disease that is left after initial therapy and can be now monitored very effectively with very, very sensitive tests.

And furthermore, there are actually drugs that can actually deal with this MRD and ALL. So in general, the prognosis of ALL patients continues to be insignificantly improving even in the older adult population as well as even in the older ALL patients, patients over the age of 65 and 75 because the number of these agents are reasonably well tolerated and less toxic and highly effective. So I think the progress in ALL therapy has been significant over the last 10 years for sure.

*Dr. Patrick Stiff:*

So Kevin, in answer to your question, it's truly about not just ALL but AML. Should you get a second and third opinion? I'm not sure you necessarily need a second or third opinion. It depends on where you go the first time. So ALL is a disease that's occupies only about one in four patients with adult acute leukemia. So it's more rare, more uncommon. And as was mentioned, there are lots of nuances that we now also manage in patients with ALL.

So I in general feel that whether it's an academic center or a standalone center with expertise, we all have doctors that just specialize in ALL as something that they predominantly handle. So we have ALL doctors, we have AML doctors and sometimes there's a little bit of a modification, but you really need to know this stuff, cold things are changing very rapidly and it was mentioned when do you use CAR T cells for ALL? When do you use the immune therapy, blinatumomab, inotuzumab?

Those are questions that I think the practicing community oncologist really doesn't know as well as somebody who really specializes in the management of these diseases. That's one of the things that, not to harp too much, but MyeloMATCH will be basically doing that at the national level and then these protocols that are going to be done, they're going to be available to community docs, but the therapy that's going to be chosen for those patients is going to be done centrally.

Whereas now there's nothing really like that for ALL. So I think for ALL especially, you really need to make sure that you have the expertise of a team that really specializes in ALL. And we can talk about some of the nuances of treatment in adults a little bit later.

*Dr. Farhad Ravandi:*

I agree. I just want to add that I really do think that patients with ALL should be initially at least evaluated at academic centers. I know it's not always easy for patients to be living near major academic centers, but I think initial evaluation is important because the academic doctors can always communicate with the local doctor and try to advise them to some degree on what's the best plan of moving forward because this is a disease that is becoming more and more curable and there is a certain degree of expertise that is needed to manage these patients.

*Dr. Patrick Stiff:*

I totally agree. In fact, in an adult the amount of residual disease you have after the first four weeks of therapy determines to a large extent your prognosis. So patients who have refractory disease because they were undertreated initially, it's almost impossible to overcome that even with some of the modern therapies.

CAR Ts may help, but again, it's the first therapy in oncology that's always true. Unfortunately, the only analogy I usually come up with is cockroaches in New York, if you let those suckers become mutant, they're tough to kill. The same happens for leukemia cells. It's not what you get treated with late, it's what you get treated with early that really determines whether or not you have a better chance or not of cure.

***Kevin Radelet:***

**Okay. Bouncing back the AML quickly, a question came up on the Q&A. What are the names of oral agents for AML?**

*Dr. Patrick Stiff:*

Well, we mentioned venetoclax, that's an oral agent in Venclexta. And then the other oral agents, hypomethylating agents, that's the class that we were talking about. azacitidine and decitabine are the parenteral drugs, and the one that's approved now for treatment in adults for especially MDS is oral cedazuridine, decitabine. And several studies have been done to show that that is as equally effective and it gets into the body as equally effective and at the right concentrations as the oral medication.

There is an oral azacitidine and it is approved as maintenance therapy for elderly patients who enter into complete remission. And it's particularly of value in a subgroup of those patients, those with an NPM1 mutation and given as maintenance improves the survival of patients after induction therapy and patients above the age of 60. So these again are the major drugs. The oral azacitidine is not approved for treatment of AML otherwise or MDS.

*Dr. Farhad Ravandi:*

And in terms of subsets of AML, there are some oral agents, but they're not generally for every patient with AML. There was a question about FLT3 gene mutated AML. For example, there are several oral agents that are approved in that disease, some in the frontline setting and some in the relapse setting. Myostatin was the one that was approved now about 10 years ago or little less than 10 years ago.

But there are others. Gilteritinib approved for relapsed FLT3 mutated AML. And then there is quizartinib that is just recently been approved for frontline setting. These are actually very effective drugs, oral agents. And there's a question about survival rate of a 19-year-old with AML with mutated gene FLT3.

I would tell you that 20 years ago, this used to be almost a guarantee of a fatal disease even though if you had a transplant, which is still absolutely necessary in first remission. But I can tell you that now with the availability of these agents, the survival has significantly improved and especially in a younger 19-year-old, we are able to cure a significant fraction of these patients.

Before we move on, there are a couple of a few other oral agents. Again, for very specific subsets, less than 20% of patients have these mutations called IDH1 or IDH2, and there are specific oral drugs for them, TIBSOVO and IDHIFA. And then there are new agents, oral agents. Again, this is in a very narrow subset of patients called KMT2A, rearranged AML or ALL actually for that matter.

And these are what we call menin inhibitors, but they're also oral agents and they haven't been approved yet, but they're very exciting. So this is just going back to what I said earlier, there is a lot of excitement about these specific agents, which either alone or particularly in combinations are going to be very effective and much, much better tolerated in general than traditional chemo, especially in the older and unfit patients.

*Dr. Patrick Stiff:*

So let me ask you a question, Dr. Ravandi. With the recent approval of quizartinib for frontline therapy of AML in July I think it was, we now have two agents, myostatin and quizartinib. What is the standard of care non protocol patients with FLT3 mutations as for your frontline therapy currently? Put you on the spot here a little bit.

*Dr. Farhad Ravandi:*

No, I am actually glad to be put on the spot. Thank you. I would actually say that I personally believe quizartinib is a more potent FLT3 inhibitor. It is a much more specific kinase inhibitor. It's specific the FLT3 protein much more specifically than myostatin does. Now there are some debates that matter. Maybe the effect of myostatin on other proteins in the frontline setting is important.

Personally, I still believe that quizartinib is probably a better, and I have absolutely no data to support what I say. But since I have been involved in the development of both these agents for 20 years and phase one studies of myostatin and phase one studies of quizartinib or early studies for the audience, I think the quizartinib is a more potent agent.

And the only issue that I may bring is that the study that led to the approval of quizartinib did have some early toxicity, particularly in the older population. And so that's why I feel that most of these strategies are best to be used at least initially in consultation with an academic center because there are now multiple options available and these can be somewhat tailor made to different patients.

*Dr. Patrick Stiff:*

I would totally agree with your assessments. And of course soon we're going to have the data on gilteritinib as part of induction therapy and we'll have to see that the decision as far as what to use down the line may depend on the results of that study. But I agree with you that quizartinib data does look very impressive. Not to say that the myostatin data is not to be considered anymore because there's been no head-to-head comparison.

***Kevin Radelet:***

**I'd just like to remind the audience real quick that you're each going to receive the recording here of today's session along with captioning that comes with it. So if you're taking notes, please continue to do so, but you're going to also get the follow up so you can come and revisit what the doctors have been talking about at a later time.**

**One of the other questions that just came up is I believe the patient was diagnosed with MDS/AML and has been in remission for three years. And the question is, can the maintenance of AZA/VEN be discontinued?**

*Dr. Farhad Ravandi:*

So this is what Dr. Stiff mentioned earlier, that AZA is azacitidine and VEN is venetoclax. And the study that was conducted in this was a very large multinational study close to about a thousand patients that clearly showed this is the current

standard of treatment for older unfit patients with AML. And I would say to you that when the study was designed, I don't think anybody had the expectations of the success of the study.

And typically in AML therapy, we treat patients for several months and then we just either, unfortunately the patient relapsed in the past or they underwent an allogeneic stem cell transplant and in the older population they weren't able to continue anyway. This regimen was effective and tolerable. So I have had patients on this regimen who have been on it for four years. Now, of course as time goes on, I reduce the number of days and make sure the patient is tolerating it very well.

But in terms of maintenance therapy, AML and continuation of therapy in AML, I think this is something that we have never really thought about a lot because in the past we didn't have tolerable agents that patients could stay on for a long time. And I think probably, and I don't know how Dr. Stiff feels about this, I think our attitude, even as practitioners may change as we develop these better tolerated strategies, and the way I tell patients is if I'm treating your high blood pressure and it gets better, I don't stop your blood pressure pill.

And so this is the way I advise my patients and I continue many of these agents. There is obviously caveats expensive as mentioned, the azacitidine, you have to come to clinic every four or five or six weeks to get it five or seven days in a row. So there are a lot of elements into it, but this is why we like to develop oral strategies that can be better managed with less frequent hospital attendance. But in terms of how long this patient should continue, I would advise them to be in close discussion with their physician and continue as long as they tolerate it.

*Dr. Patrick Stiff:*

I agree. I think if you're not going to proceed with a transplant or your transplant ineligible, that therapy should continue. It's important also in the initiation of this therapy for people who are just starting it. And we talked about why orals might be a little bit better for those patients because they're coming in so frequently.

You really need to give the treatment of full four to six cycles before you say it's not working. It doesn't work in everybody, but if you do one cycle or two cycles and say this is too hard, the first cycles are hard, hardest cycles. And then as was mentioned, we do sometimes temper the duration and the dose of these agents to make them more tolerable for patients and it seems to be as effective, but we start with the torpedoes full speed ahead for the first several cycles unless patients really get sick and it takes sometimes four to six cycles.

But what we also know is especially early on that if you do four to six cycles and you're in remission, if you stop it comes back pretty quick. So since it comes back quick for early patients in remission, we feel that for those that are in longer term remission, it's still probably going to come back. You still have the cells.

There are some sensitive tests that are available now and they're going to be more sensitive tests available in the future that will really be able to say, is there cells lurking there that you're just holding off? And until we know that and can prove that a true negative patient is not going to relapse, those are studies maybe two or three or four years from now, we always advise patients to continue it if they're tolerating it. Obviously we don't have the final results, but it's hard to get patients back into remission once they relapse.

***Kevin Radelet:***

**A question in a general sense for I think anybody that is diagnosed with leukemia, there's a participant who, her mother had it, her grandmother had it, her brother had it, and another aunt had it. So her question is, how could it not be genetic when so many generations of her family have been diagnosed?**

*Dr. Patrick Stiff:*

Well, who said it wasn't? I mean, there are some germline mutations that predispose patients to leukemia. And in fact, if patients have those germline mutations, we check the siblings. If the sibling's going to be a transplant donor because indeed donated cells from the sibling can actually eventually cause a new leukemia in the patient who gets the transplanted with those cells. So there are germline mutations.

If your doctor's telling you that, oh, don't worry about it, you're not at risk, you may be at risk. And it depends on what the germline mutations of your family are. I'm not sure there's a lot that we can do about it. Obviously there are certain things that can cause leukemia like chemicals, herbicides, pesticides, benzene, carbon tetrachloride, radiation exposures, et cetera. So you want to try to minimize your exposure to those.

But there are germline mutations associated with leukemia. And yes, unfortunately you may be at risk. Dr. Ravandi, would you advise doing a bone marrow on this patient or this person who doesn't have leukemia and look for these germline mutations?

*Dr. Farhad Ravandi:*

Yes, definitely. When there is a strong family history, and particularly if the leukemia develops in a young patient with a lot of family members and close family members, we do have a genetic counseling clinic which really specializes in this. I would still say that the vast majority of AML patients probably have the disease developed de novo without a high impact of any germline predisposition. But this is the beginning of the field.

We are beginning to understand more and more about these predisposing mutations because again, it's a very young field. As you know, in other cancers, this has become even much more established. Definitely, there's no question that I believe there is an interplay of genetics and environment in developing cancers. But again, I think the vast majority of leukemia is developing the older population for a reason, not based on family predisposition to that extent,

***Kevin Radelet:***

**Having learned that, how do you request a bone marrow biopsy? I mean, do you just go back to your primary or how would you request such a thing?**

*Dr. Farhad Ravandi:*

The bone marrow biopsy is always done anyway in a patient with suspected AML. The genetic counseling is that somebody with the expertise of these genes. And also you have to remember that you have to establish, as mentioned, that these are germline. Germline means that they exist in the entire population of cells in a patient.

As in specific genetic change or aberration or whatever you want to call it, is not just developing in the bone marrow cells that became leukemia, but they existed and they continue to exist everywhere. And for that, we need to do other biopsies, for example, a skin biopsy or... The ways to establish that this mutation actually is present in the entire patient and not just in the leukemic cells.

*Dr. Patrick Stiff:*

So of course at this point in time, we have no therapies for these. So I mean there is the drawback, it is like some patients with genetic diseases like I can't recall if Lou Gehrig's is a disease that you can diagnose early, but sometimes knowing and not knowing are decisions that really should be made very carefully with somebody like a genetics counselor and yourself to say, okay, if I have this germline mutation and they're not going to treat it, why not just not know it and be comfortable with trying

to minimize my risk of change? And if something does happen to seek medical attention very quickly.

I'll also say that some of these germline mutations are also associated with cardiac disease, so coronary artery disease and heart disease. So anybody who might have a family history of leukemia and if they also have a history of coronary artery disease, that's something that they should potentially pursue as well.

***Kevin Radelet:***

**Another question just came up that I'll just read it the way they wrote it. It says how often maintainable treatment is given and the names of sensitive tests?**

Dr. Farhad Ravandi:

I'm sorry.

Kevin Radelet:

I'm not sure exactly what they're getting at it.

*Dr. Farhad Ravandi:*

How often should it be given?

*Dr. Patrick Stiff:*

So I think they were talking about, we said that ultimately we might be able to diagnose, so these are very sensitive NGS type testing. There are some experimental ones that are being developed and looking for mutations on a single strand or both strands of the DNA that might be able to help us clearly identify one leukemia cell in the million. And we can do that now for ALL. We can do that in multiple myeloma and the lower the number of cells even down to one in a million.

So you do a bone marrow test and if you detect one or two cells in a million, your prognosis is not as good as if you detect zero cells in a million. We're not there with AML yet and it may not be as important, but those are tests that should be done in patients with ALL for sure.

And again, I'll give credit to MD Anderson who's really done a lot of work in this area and has modified our thinking about who should get transplants and who shouldn't get transplants for ALL because there was a period about 10 years ago where if you had ALL and you were an adult, you got a transplant. Now we've been able to really scale that back and some of the tests that we use for minimal residual disease are guiding us for ALL decision-making.

***Kevin Radelet:***

**Just in general for acute leukemias, how is the severity of the disease determined and are there different levels of severity?**

*Dr. Farhad Ravandi:*

There is no such a thing as severity or staging for leukemia. Unfortunately, I tell my patients that leukemia is always stage four, and when you talk about breast cancer, you talk about advanced because your blood and your bone marrow is everywhere from the beginning. Now, there are ways that you can define how easily curable AML is, and that again goes back to the molecular and genetic assessment.

At diagnosis, we look at these bone marrow leukemic cells and the neurologists look at their chromosomes and genes. And there are these chromosome and gene abnormalities that have been actually cataloged over many years by large cooperative groups in the U.S., CLGB, SWAG, the British groups all around the world that have defined that some subtypes of AML are much more likely to be curable with the traditional chemotherapy.

Other types are much, much more difficult and they tend to have more significant of these chromosome and gene abnormalities and some specific gene abnormalities are still unfortunately highly incurable. There is a gene called P53 when it is significantly mutated in the patient, it is still extremely difficult to cure those patients.

And this is also very important in terms of therapy decision making because even now, despite the fact that I mentioned we have these gene directed oral therapeutic strategies, we still perform allogeneic stem cell transplant in first remission for patients who have a more difficult AML. And unfortunately that still is the case for a significant majority of patients who are young enough, fit enough and have a donor who can go on to have a transplant in first remission.

*Dr. Patrick Stiff:*

I agree, I think there was one question about elderly patients undergoing transplant and the same decision-making goes while most elderly patients, the reason the prognosis is worse for elderly patients is not just because they're not as fit in tolerating therapy, but because the adverse genetic abnormalities are more common in the elderly.

But occasionally, we come across a patient who has actually good genetic abnormalities and we would not consider transplant in that patient, but the age of transplant is gradually moved up because we're having better and better

treatments for infections that patients gets. We have better and better assessments of patients before transplant to know which patients are going to have more complications. And we use that in the consideration. And again, the genetic abnormality.

And one of the things that's really popped up in the last few years is after initial therapy, does the patient still have residual disease? Or in remission, their bone marrow looks great, but they still have one of these minimal residual disease tests that shows that they have a residual leukemia, and those patients have a poor outcome even with transplant.

And therefore we're really focusing now more and will be in this new MyeloMATCH organization on trying to get those patients to an MRD negative state and hopefully improve the transplant outcome for patients of all age. But we have gradually moved up our age. It used to be when I first started way, way back, it was 35 and then it was 40 and then it was 50 and then it was 60 and then 70.

And we recently had a talk from somebody who's transplanting patients in their early 80s. And again, you have to be in a good physical shape for that, but there are centers that are willing to transplant those patients. There are a lot of requirements that we use not just in the genetics, but also what's their heart function, what's their kidney function, how are their lungs doing? What's going on with their liver? Have they had a heart attack? Do they have atrial fibrillation? Are they depressed? Do they have a good caregiver?

All these things enter into decision making process of whether or not a transplant's going to benefit a patient. So the age is still a soft requirement, but it's not as hard as it used to be.

*Dr. Farhad Ravandi:*

I'd just like to add that the same way as we mentioned about all these new treatments and being effective and better tolerated, transplants have become better tolerated and more effective in many ways. So I don't want to give the audience the impression that we are trying to move away from transplants. Still transplant is a necessity in, well, I would say many if not most patients with AML in first remission, probably less so in ALL, but please do not take a message from the stock that the doctors said, we have very effective treatments and transplant is no longer needed.

***Kevin Radelet:***

**In a general sense, again, do we know what the common root causes for acute leukemias might be?**

*Dr. Farhad Ravandi:*

It was mentioned that there is a small population that have genetic, at least to our current knowledge, smaller population that have a predisposing genetic aberrations. But the majority of patients, probably environmental factors such as exposure to benzene products. There are some professions that increase the likelihood of developing AML, typically chemical or petrochemical industry.

And of course there is an element of it associated with aging. As I mentioned earlier, the majority of patients are over the age of 50 and half of the patients are over the age of close to 70. So that per se, unfortunately predispose us to develop not only leukemia, but also other cancers.

*Dr. Patrick Stiff:*

So there are of course, well-known treatments that we use for other cancers like Hodgkin's disease, non-Hodgkin's lymphoma, even breast cancer that do predispose patients to getting a secondary cancer. They're called treatment related AMLs and MDS. Our colleagues who treat solid tumors are more in tune with this, and they also have more targeted therapies that are less potentially toxic.

But herbicides, pesticides, if you're in an area that has high rate on and you spend a lot of time in the basement, probably not good to do that. Any radiation exposure also is not bad. Chemicals used for industrial cleaning, chemicals used for photography, et cetera. You need to have a mask on that prevents you from inhaling those and having good ventilation. Those are things that I think are important.

These diseases are seemingly becoming more common because we've polluted our atmosphere. And again, that's why older patients get leukemias. The pediatric tumors are probably more genetic. The older patients with cancers are more related to our environment. Same thing goes for colon cancer, same thing goes for gastric cancer and probably even a bit for breast cancer.

***Kevin Radelet:***

***Wow, interesting. Is there any kind of special diet that a patient should observe or practice when they're undergoing treatment?***

*Dr. Farhad Ravandi:*

So for a long time there was a thought that maybe patients should avoid fresh fruits and vegetables while they're getting chemotherapy. And actually we did a study here in MD Anderson not quite a few years ago where we'd randomized patients to regular diet, whatever they wish to have versus those who had that restricted diet. And really there was no difference in the rate of infections or type of infections.

I do however recommend, we still do recommend that patients, if they're going to have vegetables and fruits, et cetera, they should wash them very carefully at home. And I advise patients not to go to the salad bars in a fast food restaurant and have those things. And also I would advise them not to have raw food, sushi and raw meat, et cetera. Highly advise not to have those.

In terms of quality of diet, I think for all of us, the better quality of diet is the way we should go. And this applies to whether we are getting chemotherapy for any disease or just living a normal life. So there is no specific diet that can protect against leukemia or cancer, except for the fact that the healthier we eat, the better off we are.

*Dr. Patrick Stiff:*

Yes, I would say that's exactly true for patients in our age group, especially my age group, it's too late to change your diet and hope that it's going to change your cancer risk. Healthy food should be provided for kids and grandkids, et cetera. And again, stay away from your favorite greasy spoon.

I have patients say, my whole family ate there and I was the only one that got sick. Well, it's because your intestines are more sensitive to bacteria that might be seen in food that's not prepared very well, et cetera. So things that are cooked just for you like a steak or a pizza are better than, as was mentioned, a salad bar or a buffet where things have been sitting there for hours and people might've coughed on them. Who knows?

***Kevin Radelet:***

**Yeah. Interesting. Are there specific symptoms or side effects that are red flags that you should make sure you tell your doctor about right away**

*Dr. Patrick Stiff:*

On treatment or just in coming up with a diagnosis?

*Dr. Farhad Ravandi:*

Fever is the most important symptom that you should tell your doctor right away. And if you've received recent therapy, even if you have a fever at 3:00 AM you need to be in an emergency room at 3:30 because the biggest thing that even with the more tolerable recent regimens, the biggest thing that happens is reduction of your blood counts, your white cell count and your ability to fight infections gets suppressed. So if you have any form of infection, this has to be managed rapidly with effective antibiotics.

The reason why we've actually had so much progress in leukemia therapy, it's not just because of better drugs, but also because of better anti effective agents. Antibacterial, antiviral and antifungal particularly, especially in the south where we are in Texas and Houston, fungal infections can be a major problem. And so at the moment you have any form of symptoms that suggestive of you having an infection, particularly fever, you should see a doctor immediately.

*Dr. Patrick Stiff:*

And also bleeding with patients with low platelet counts have mostly what we call mucosal bleeding. So nose bleeds or gum bleeding or spots on their legs, which we call petechiae. Those are things that should bring to the attention of the doctors. And anybody who's getting therapy that might have low blood counts, if they fall and hit their heads, they definitely need to seek out an evaluation because they could end up with a slow but serious bleed and not have symptoms initially, but could potentially have a very serious problem that they left get out of control. So those are the other things.

And of course some of these medications, there was a question about diarrhea. Some of them cause diarrhea. Some of these new medications, especially oral drugs can cause diarrhea. And there are tricks of the trade, if you will, that we use sometimes to help manage patients with the diarrhea or constipation. And again, be sure to bring it up with your doctor. I think a lot of times patients who are on these therapies don't tell us what's really going on because they're afraid we're going to slow it down or stop it or take a break.

And they don't want to do that because they're worried about relapsing or not getting into remission. But indeed, talk to your physicians about these and basically if you're concerned that the diarrhea is there, but it's not horrible and let's try this and this and this, please don't stop my drugs. I'm worried about relapse. That does enter into the equation because we all have had diarrhea and or nausea. And if it's something that's working and helping you, especially if it's going to be time limited, it may actually be worthwhile just to focus on symptom control rather than prevention.

***Kevin Radelet:***

**Well, we are getting a little short on time and very much appreciate the time that you two have taken out to help us today. There is one thing that I'd like to share on the screen, which is our website. Can you see that?**

If you go to our website, ***leukemiarf.org***, you'll see up here we have a dropdown, which is clinical trials. We're very proud that we have just launched our Clinical Trials Hub and there's all kinds of information on here, background information, but perhaps the nicest thing are these two down here at the bottom, the LRF online search tool where you can answer just a few short questions. And this is all very specific to leukemia.

There's of course clinicaltrials.gov, which is a Monster website, but we're very happy that we're able to offer this to our patients to give them more background information on the clinical trials. So I do urge those that are listening with us today to visit our website if clinical trials becomes a discussion with your doctor and you can learn quite a bit just by going to this one page.

So that said, thank you again, Dr. Ravandi, dr. Stiff. Again, a reminder to those that are listening in, you will get a copy of the recording today. I'm also going to be sending out a short questionnaire, taking you two or three minutes to fill it out. And it's very helpful to us in terms of how we can improve the program offerings that we're putting out there. And with that, we will call it a day. We thank you all very much and we will be in touch moving forward.